

**REPLY AND AMENDMENT**

Atty. Dkt. No. 0618.004.0002

Serial No.: 10/071,512

Filing Date: February 8, 2002

Title: Methods of Light Activated Release of Ligands from Endosomes

**REMARKS/ARGUMENTS****I. SUPPORT FOR THE NEWLY PRESENTED CLAIMS**

Claims 1, 2, 12-18, 24, 25 and 43-54, which were pending, have been canceled and new claims 55-94 have been introduced.

Support for the newly presented claims 55-94 can be found throughout the specification and figures, as well as the originally presented claims. Specifically, support for new independent claims 55 and 72 can be found in at least paragraphs 0011, 0034, 0055, 0065, 0089, 0106, 0114 and 0122 of the specification. Support for new claims 56 and 73 can be found in at least paragraph 0068. Support for new claims 57 and 74 can be found in at least paragraph 0055. Support for new claims 58, 59, 75 and 76 can be found in at least paragraph 0115. Support for new claims 60 and 83 can be found in at least paragraph 0019 and originally presented claim 17. Support for new claims 61, 62, 67, 68, 84, 85, 90 and 91 can be found in at least paragraph 0106. Support for new claims 63, 64, 69, 70, 86, 87, 92 and 93 can be found in at least paragraph 0015. Support for new claims 65, 71, 88 and 94 can be found in at least paragraph 0016 and originally presented claims 14 and 30. Support for new claims 66 and 89 can be found in at least paragraph 0120. Support for new claims 77 and 78 can be found in at least paragraph 0084. Support for new claims 79, 80 and 81 can be found in at least paragraphs 0090 and 0091. Support for new claim 82 can be found in at least paragraph 0089. Accordingly, no new matter has been introduced by way of these new claims.

**II. THE REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH ARE NOW MOOT**

In the Office Action dated March 29, 2005, the Examiner rejected previously pending claims 12, 13, 24 and 25 under 35 U.S.C. §112, second paragraph, as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." *Prosecution History of U.S. Serial No. 10/071,512, Office Action of March 29, 2005*, page 2. Without agreeing with the Examiner's assertions that previously pending claims

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12, 13, 24 and 25 are indefinite, Applicant has canceled these claims and presented new claims to better capture envisioned commercial embodiments. Accordingly, the rejections of claims 12, 13, 24 and 25 under 35 U.S.C. §112, second paragraph are now moot. Reconsideration and withdrawal of this rejection are earnestly solicited.

**III. THE REJECTIONS UNDER 35 U.S.C. §102 ARE NOW MOOT****A. THE REJECTION OF CLAIMS 1, 2, 12, 13, 17, 18, 43 AND 49 UNDER 35 U.S.C. §102(b) IS MOOT**

In the Office Action of March 29, 2005, the Examiner rejected claims 1, 2, 12, 13, 17, 18, 43 and 49 under 35 U.S.C. §102(b) as allegedly "being anticipated by Berg et al (WO 96/07432, published 3/14/96) ["Berg PCT"]...." *Office Action*, page 3. Without agreeing with the Examiner's assertions that claims 1, 2, 12, 13, 17, 18, 43 and 49 are anticipated, Applicant has canceled these claims and presented new claims to better capture envisioned commercial embodiments. Accordingly, the rejection of claims 1, 2, 12, 13, 17, 18, 43 and 49 is now moot.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Vertegaal Bros. v Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The Examiner alleges that the Berg PCT teaches "a method for releasing molecules into the cytosol of cells by ... treating the cells with a fluorescent photosensitizer that is conjugated to the molecule to be released, ... and exposing the cells to a light of a wavelength that excites the fluorescent photosensitizer,...." *Office Action*, text bridging pages 3 and 4. The Examiner also states that "molecules for release include oligonucleotides such as ribozymes. ... [and] ribozymes are double-stranded to the extent that ribozymes form intrastrand double helices." *Office Action*, page 4. The Berg PCT, however, does not teach or suggest any method of delivering and releasing a double-stranded oligomer of between about 20-30 nucleotides in length into the cytosol of a cell. Because the Berg PCT does not recite each and every claim limitation of the currently presented claims, the Berg PCT does not anticipate the present claims.

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New claims 72-94 recite contacting a cell with a fluorescently labeled transport peptide to deliver and release at least one oligomer into the cytosol of a cell. The Berg PCT, however, does not teach or suggest the use of a fluorescently labeled transport peptide in delivering and releasing oligomers into the cytosol of a cell. Because the Berg PCT does not teach each and every element of the currently claimed invention, the Berg PCT does not anticipate the currently claimed invention.

In addition, Applicant asserts that the Berg PCT fails to enable any method of delivering or releasing any type of oligomer into the cytosol of a cell using a fluorescent molecule. And “to serve as an anticipating reference, the reference must enable that which it is asserted to anticipate. ‘A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled.’” *Elan Pharms., Inc. v. Mayo Found.*, 346 F.3d 1051, 1054 (Fed. Cir. 2003) (emphasis added) (quoting *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, (Fed. Cir. 2003)). The Berg PCT is completely silent in describing how to make and use a method of releasing an oligomer into the cytosol of the cell. Applicant asserts that one of skill in the art, after reading the Berg PCT would be unable to practice methods of delivering and releasing an oligomer into the cytosol of a cell comprising the use of a fluorophore, without undue experimentation. Accordingly, the Berg PCT did not anticipate the previously presented claims, nor does the Berg PCT anticipate the currently presented claims. Reconsideration and withdrawal of this rejection are earnestly solicited.

**B. THE REJECTION OF CLAIMS 1, 2, 12, 13, 17, 18, 24, 25, 43, 45, 48, 49, 52 AND 53 UNDER 35 U.S.C. §102(e) IS MOOT**

In the Office Action of March 29, 2005, the Examiner rejected claims 1, 2, 12, 13, 17, 18, 24, 25, 43, 45, 48, 49, 52 and 53 under 35 U.S.C. §102(e) as allegedly “being anticipated by Berg et al (US Patent 6,680,301, issued 1/20/04) [Berg ‘301]....” *Office Action*, page 4. Without agreeing with the Examiner’s assertions that claims 1, 2, 12, 13, 17, 18, 24, 25, 43, 45, 48, 49, 52 and 53 are anticipated, Applicant has canceled these claims and presented new claims to better

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capture envisioned commercial embodiments. Accordingly, the rejection of claims 1, 2, 12, 13, 17, 18, 24, 25, 43, 45, 48, 49, 52 and 53 is now moot.

The Examiner alleges that Berg '301 teaches "a method for releasing molecules into the cytosol of cells by ... treating the cells with a fluorescent photosensitizer that is conjugated to the molecule to be released, ... and exposing the cells to a light of a wavelength that excites the fluorescent photosensitizer,...." *Office Action*, page 4. Applicant respectfully disagrees with the Examiner's assertions regarding the teachings of Berg '301.

Claim 55 and its dependants recite methods of delivering and releasing at least one double-stranded oligomer of between about 20-30 nucleotides in length into the cytosol of one or more cells. Berg '301, however, does not teach or suggest any method of delivering and releasing a double-stranded oligomer of between about 20-30 nucleotides in length into the cytosol of a cell. Because Berg '301 does not recite each and every claim limitation of the currently presented claims, Berg '301 does not anticipate the present claims.

New claims '72-94 recite contacting a cell with a fluorescently labeled transport peptide to deliver and release at least one oligomer into the cytosol of a cell. Berg '301, however, does not teach or suggest the use of a fluorescently labeled transport peptide in delivering and releasing oligomers into the cytosol of a cell. Because Berg '301 does not teach each and every element of the currently claimed invention, Berg '301 does not anticipate the currently claimed invention.

In addition, Applicant asserts that, although Berg '301 contains additional material over the Berg PCT, Berg '301 also fails to enable any method of delivering or releasing any type of oligomer into the cytosol of a cell using a fluorescently labeled transport peptide. Berg '301 is completely silent in describing how to make and use a method of releasing an oligomer into the cytosol of the cell using a fluorescently labeled transport peptide. Applicant asserts that one of skill in the art, after reading Berg '301 would be unable to practice methods of delivering and releasing an oligomer into the cytosol of a cell comprising the use of a fluorescently labeled transport peptide, without undue experimentation. Accordingly, Berg '301 does not anticipate

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the currently presented claims. Reconsideration and withdrawal of this rejection are earnestly solicited.

**IV. THE REJECTIONS UNDER 35 U.S.C. §103 ARE NOW MOOT****A. THE REJECTION OF CLAIMS 1, 2, 15, 18, 43, 47, 49 AND 51 UNDER 35 U.S.C. §103 OVER BERG '301 AND IN VIEW OF PRIEST IS NOW MOOT**

In the Office Action dated March 29, 2005, the Examiner rejected claims 1, 2, 15, 18, 43, 47, 49 and 51 under 35 U.S.C. §103 as allegedly being obvious "over ... Berg et al (US Patent 6,680,301, issued 1/20/04) in view of Priest (US Patent 5,391,723, issued 2/21/95)." *Office Action*, page 6. Without agreeing with the Examiner's assertions that claims 1, 2, 15, 18, 43, 47, 49 and 51 are obvious, Applicant has canceled these claims and presented new claims to better capture envisioned commercial embodiments. Accordingly, the rejection of claims 1, 2, 15, 18, 43, 47, 49 and 51 is now moot.

Applicant asserts that the combination of Berg '301 and Priest does not render the newly presented claims obvious. To establish a case of *prima facie* obviousness, the Examiner must meet three criteria. First, the Examiner must show that the references upon which she or he relied teach *every* limitation of the currently claimed invention, *In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974). Second, the Examiner must show that there is some suggestion or motivation in the references themselves, or within the knowledge of one of ordinary skill in the art, to combine the references to arrive at the claimed invention. Lastly, the Examiner must show that there is a reasonable expectation of success in combining the references, and that this expectation of success is found in the references as well. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

Applicant asserts that the cited art, alone or in combination, neither teach each and every limitation of the currently claimed invention, nor provide any teaching, suggestion or motivation to combine the cited art to arrive at the claimed invention, with a reasonable expectation of success. Specifically, claims 55-71 recite methods of delivering and releasing at least one double-stranded oligomer of between about 20-30 nucleotides in length into the cytosol of a cell.

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In addition, new claims 72-94 recite contacting a cell with a fluorescently labeled transport peptide to deliver and release at least one oligomer into the cytosol of a cell. As detailed above, Berg '301 does not teach or suggest a method of delivering an oligomer into the cytosol of a cell, nor does Berg '301 teach or suggest the use of a fluorescently labeled transport protein, and Priest does not cure these deficiencies. The Examiner cites Priest because Priest allegedly teaches "the use of pH-sensitive covalent linkers to attach double-stranded oligomers to targeting protein." *Office Action*, page 6. The combination of Berg '301 and Priest, however, still does not teach a method of delivering an oligomer of between about 20-30 nucleotides into the cytosol of a cell, nor does the combination teach or suggest the use of a fluorescently labeled transport protein.

Furthermore, there is no motivation found in the references to combine Berg '301 and Priest, with a reasonable expectation of success. Specifically, there is no "teaching or suggestion in the references to support their use in the particular claimed invention." *Smithkline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 887, (Fed. Cir. 1988). Accordingly, Applicant asserts the combination of Berg '301 and Priest cannot be used to establish a *prima facie* case of obviousness against the currently presented claims. Reconsideration and withdrawal of the Examiner's rejection are earnestly solicited.

**B. THE REJECTION OF CLAIMS 1 AND 14 UNDER 35 U.S.C. §103 OVER BERG '301 AND IN VIEW OF PARKER IS NOW MOOT**

In the Office Action dated March 29, 2005, the Examiner rejected claims 1 and 14 under 35 U.S.C. §103 as allegedly being obvious "over ... Berg et al (US Patent 6,680,301, issued 1/20/04) in view of Parker et al (US Patent 4,541,438, issued 9/17/85)." *Office Action*, page 7. Without agreeing with the Examiner's assertions that claims 1 and 14 are obvious, Applicant has canceled these claims and presented new claims to better capture envisioned commercial embodiments. Accordingly, the rejection of claims 1 and 14 is now moot.

In addition, the combination of Berg '301 and Parker does not render the newly presented claims obvious. Applicant asserts that the cited art, alone or in combination, neither teach each

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and every limitation of the currently claimed invention, nor provide any teaching, suggestion or motivation to combine the cited art to arrive at the claimed invention, with a reasonable expectation of success. As detailed above, Berg '301 does not teach or suggest a method of delivering an oligomer into the cytosol of a cell, nor does Berg '301 teach or suggest the use of a fluorescently labeled transport protein, and Parker does not cure these deficiencies. The Examiner cites Parker because Parker allegedly teaches "an endoscopic light source capable of delivering excitatory wavelengths of light ...." *Office Action*, page 7. The combination of Berg '301 and Parker, however, still does not teach or suggest a method of delivering an oligomer of between about 20-30 nucleotides into the cytosol of a cell, nor does the combination teach the use of a fluorescently labeled transport protein.

Furthermore, there is no motivation found in the references to combine Berg '301 and Parker, with a reasonable expectation of success. Accordingly, Applicant asserts the combination of Berg '301 and Parker cannot be used to establish a *prima facie* case of obviousness against the currently presented claims. Reconsideration and withdrawal of the Examiner's rejection are earnestly solicited.

**C. THE REJECTION OF CLAIMS 1 AND 16 UNDER 35 U.S.C. §103 OVER BERG '301 AND IN VIEW OF FLOWER IS NOW MOOT**

In the Office Action dated March 29, 2005, the Examiner rejected claims 1 and 16 under 35 U.S.C. §103 as allegedly being obvious "over ... Berg et al (US Patent 6,680,301, issued 1/20/04) in view of Flower et al (US Patent 6,443,976, issued 9/2/02)." *Office Action*, page 8. Without agreeing with the Examiner's assertions that claims 1 and 16 are obvious, Applicant has canceled these claims and presented new claims to better capture envisioned commercial embodiments. Accordingly, the rejection of claims 1 and 16 is now moot.

In addition, the combination of Berg '301 and Flower does not render the newly presented claims obvious. Applicant asserts that the cited art, alone or in combination, neither teach each and every limitation of the currently claimed invention, nor provide any teaching, suggestion or motivation to combine the cited art to arrive at the claimed invention, with a reasonable

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expectation of success. As detailed above, Berg '301 does not teach or suggest a method of delivering an oligomer into the cytosol of a cell, nor does Berg '301 teach or suggest the use of a fluorescently labeled transport protein, and Flower does not cure these deficiencies. The Examiner cites Flower because Flower allegedly teaches "radiation absorbing dyes such as fluorescein ...." *Office Action*, page 9. The combination of Berg '301 and Flower, however, still does not teach or suggest a method of delivering an oligomer of between about 20-30 nucleotides into the cytosol of a cell, nor does the combination teach the use of a fluorescently labeled transport protein.

Furthermore, there is no motivation found in the references to combine Berg '301 and Flower, with a reasonable expectation of success. Accordingly, Applicant asserts the combination of Berg '301 and Flower cannot be used to establish a *prima facie* case of obviousness against the currently presented claims. Reconsideration and withdrawal of the Examiner's rejection are earnestly solicited.

**D. THE REJECTION OF CLAIMS 1, 18, 44 AND 50 UNDER 35 U.S.C. §103 OVER BERG '301 AND IN VIEW OF FURUSAKO IS NOW MOOT**

In the Office Action dated March 29, 2005, the Examiner rejected claims 1, 18, 44 and 50 under 35 U.S.C. §103 as allegedly being obvious "over ... Berg et al (US Patent 6,680,301, issued 1/20/04) in view of Furusako et al (US Patent 6,251,873, issued 6/26/01)." *Office Action*, page 10. Without agreeing with the Examiner's assertions that claims 1, 18, 44 and 50 are obvious, Applicant has canceled these claims and presented new claims to better capture envisioned commercial embodiments. Accordingly, the rejection of claims 1, 18, 44 and 50 is now moot.

In addition, the combination of Berg '301 and Furusako does not render the newly presented claims obvious. Applicant asserts that the cited art, alone or in combination, neither teach each and every limitation of the currently claimed invention, nor provide any teaching, suggestion or motivation to combine the cited art to arrive at the claimed invention, with a reasonable expectation of success. As detailed above, Berg '301 does not teach or suggest a



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method of delivering an oligomer into the cytosol of a cell, nor does Berg '301 teach or suggest the use of a fluorescently labeled transport protein, and Furusako does not cure these deficiencies. Indeed, the combination of Berg '301 and Furusako, however, still does not teach or suggest a method of delivering an oligomer of between about 20-30 nucleotides into the cytosol of a cell, nor does the combination teach or suggest the use of a fluorescently labeled transport protein.

Furthermore, there is no motivation found in the references to combine Berg '301 and Priest, with a reasonable expectation of success. Accordingly, Applicant asserts the combination of Berg '301 and Furusako cannot be used to establish a *prima facie* case of obviousness against the currently presented claims. Reconsideration and withdrawal of the Examiner's rejection are earnestly solicited.

**E. THE REJECTION OF CLAIMS 1, 18, 43, 46 AND 54 UNDER 35 U.S.C. §103 OVER BERG '301 AND IN VIEW OF BURKLY IS NOW MOOT**

In the Office Action dated March 29, 2005, the Examiner rejected claims 1, 18, 43, 46 and 54 under 35 U.S.C. §103 as allegedly being obvious "over ... Berg et al (US Patent 6,680,301, issued 1/20/04) in view of Burkly et al (US Patent 6,616,826 [*sic*, 6,616,926], issued 9/9/03)." *Office Action*, page 11. Without agreeing with the Examiner's assertions that claims 1, 18, 43, 46 and 54 are obvious, Applicant has canceled these claims and presented new claims to better capture envisioned commercial embodiments. Accordingly, the rejection of claims 1, 18, 43, 46 and 54 is now moot.

In addition, the combination of Berg '301 and Burkly does not render the newly presented claims obvious. Applicant asserts that the cited art, alone or in combination, neither teach each and every limitation of the currently claimed invention, nor provide any teaching, suggestion or motivation to combine the cited art to arrive at the claimed invention, with a reasonable expectation of success. As detailed above, Berg '301 does not teach or suggest a method of delivering an oligomer into the cytosol of a cell, nor does Berg '301 teach or suggest the use of a fluorescently labeled transport protein, and Burkly does not cure these deficiencies. The

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Examiner cites Burkly because Burkly allegedly teaches that "polylysine and TAT peptides function as gene delivery systems when complexed with nucleic acids." *Office Action*, page 12. The combination of Berg '301 and Burkly, however, still does not teach or suggest a method of delivering an oligomer of between about 20-30 nucleotides into the cytosol of a cell, nor does the combination teach or suggest the use of a fluorescently labeled transport protein.

Furthermore, there is no motivation found in the references to combine Berg '301 and Burkly, with a reasonable expectation of success. Accordingly, Applicant asserts the combination of Berg '301 and Burkly cannot be used to establish a *prima facie* case of obviousness against the currently presented claims. Reconsideration and withdrawal of the Examiner's rejection are earnestly solicited.

**F. THE REJECTION OF CLAIMS 1, 18, 43, 46 AND 54 UNDER 35 U.S.C. §103 OVER BERG '301 AND IN VIEW OF BURKLY AND ROSENECKER IS NOW MOOT**

In the Office Action dated March 29, 2005, the Examiner rejected claims 1, 18, 43, 46 and 54 under 35 U.S.C. §103 as allegedly being obvious "over ... Berg et al (US Patent 6,680,301, issued 1/20/04) in view of Burkly et al (US Patent 6,616,826, [*sic*, 6,616,926] issued 9/9/03) and Rosenecker et al (US Published Application 20030125242)." *Office Action*, page 12. Without agreeing with the Examiner's assertions that claims 1, 18, 43, 46 and 54 are obvious, Applicant has canceled these claims and presented new claims to better capture envisioned commercial embodiments. Accordingly, the rejection of claims 1, 18, 43, 46 and 54 is now moot.

In addition, the combination of Berg '301, Burkly and Rosenecker do not render the newly presented claims obvious. Applicant asserts that the cited art, alone or in combination, neither teach each and every limitation of the currently claimed invention, nor provide any teaching, suggestion or motivation to combine the cited art to arrive at the claimed invention, with a reasonable expectation of success. As detailed above, Berg '301 does not teach or suggest a method of delivering an oligomer into the cytosol of a cell, nor does Berg '301 teach the use of a fluorescently labeled transport protein, and Burkly and Rosenecker do not cure these

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deficiencies. The Examiner cites Burkly because Burkly allegedly teaches that "polylysine and TAT peptides function as gene delivery systems when complexed with nucleic acids." *Office Action*, page 13. The Examiner cites Rosenecker because Rosenecker allegedly teaches that "HIV-TAT, Antennapedia and Transportan were functionally equivalent for the purpose of transferring molecules into cells." *Office Action*, page 13. The combination of Berg '301, Burkly and Rosenecker, however, still does not teach or suggest a method of delivering an oligomer of between about 20-30 nucleotides into the cytosol of a cell, nor does the combination teach or suggest the use of a fluorescently labeled transport protein.

Furthermore, there is no motivation found in the references to combine Berg '301, Burkly and Rosenecker, with a reasonable expectation of success. Accordingly, Applicant asserts the combination of Berg '301, Burkly and Rosenecker cannot be used to establish a *prima facie* case of obviousness against the currently presented claims. Reconsideration and withdrawal of the Examiner's rejection are earnestly solicited.

**Conclusion**

To better capture envisioned commercial embodiments, Applicant has canceled the previously pending claims and has presented new claims 55-94. Support for the new claims can be found throughout the specification and originally presented claims; thus no new matter has been added by way of these newly presented claims.

Presentation of new claims 55-94 renders moot the Examiner's previous claim rejections. Specifically, Applicant believes that the currently presented claims comply with, among other requirements, 35 U.S.C. § 112, second paragraph, and are not anticipated under 35 U.S.C. § 102(b) or (e), or obvious under 35 U.S.C. § 103. Reconsideration and withdrawal of the rejections are earnestly solicited.

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Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, he or she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date August 27, 2005By Todd B. Buck

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being facsimile transmitted to the USPTO or is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 29th day of August, 2005

Name

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Signature

Todd B. Buck